July 15, 1959

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Dear Peter:

Promptly to yours of the 11th.

I am happy to take up the three points you refer to. Undoubtedly, many more are going to arise.

I would not be too alarmed at having to explain Mendelian genes influencing immunological performance until the two cautions of the last paragraph of A4 have been adequately dealt with. If we have to go beyond this, I should say that a random configuration of nucleotides, in a restricted segment, might sometimes fail to encompass all possible antibody configurations. The homogeneous carrier segments into which the specific segment is inserted might also limit the overall possibilities. But I would suspect that the main effects are due to a fortuitous tie-in with autotolerance.

I had a chance to talk with Avrion about your other point on this paragraph. I would stress that the mutations in the stem line and the subsequent stepwise maturation of the progeny cells are continuous processes. At any moment, therefore, the organism should contain cells which have already mutated to a given configuration but not yet had time for its phenotypic expression. These mutants, already formed, might then be available for the prompt revival of reactivity when the antigen is no longer ubiquitous.

I am sorry for the ambiguity in paragraph 3 of A3. I am afraid I just do not agree with Burnet as you quote him on this particular subject. Yes, I do mean that somatic mutation is one of several possible kinds of differentiation and concur with you that it is a most farfetched possibility for morphogenetic inductions other than those involved in antibody synthesis. I probably should have left this out all together. That it is in here at all, is probably a carry over from the discussion at Gatlinburg where I had taken such pains to infer that the orderliness of differentiation precluded a process of nucleotide alteration. I still think it does but found that I had to admit that nucleotide alterations might be involved if they occurred at random and were then elected. I don't think I take this possibility, for the general problem of differentiation, any more seriously than you do.

Thank you for bringing Milgrom's paper to my attention. It does raise a number of important issues -- so much so that I would hesitate to build too far on such a fragmentary statement as appears in the abstracts. Certainly it would be a most informative experiment to

find out whether the skin of the unreactive guinea pigs is capable of neutralizing added toxin and if so, whether by an antibody-neutralization or an enzymatic-degradation mechanism. My only other thought is that the toxicity he is looking at is not the typical cytotoxicity, but some sort of hypersensitivity reaction dependent on the presence of homologous immune cells, or a minimal level of antibody, in the host. But why linger too long over so detailed a speculation when the experiment that suggests itself seems so straight forward.

As ever,

Joshua Lederberg